Decreased circulating levels of il-22 in newly diagnosed metabolic syndrome patients

Interleukin-22, metabolic syndrome

Hakki Yilmaz
Department of Internal Medicine, Section of Nephrology,
Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Health Science University, Ankara, Turkey

Abstract

Aim: Metabolic syndrome (MetS) is characterized by abdominal obesity, dyslipidemia, low-grade inflammation, insulin resistance, and hypertension that can lead to diabetes and cardiovascular disease. IL-22 is a member of the IL-10 cytokine family that has been shown to prevent or reverse obesity-induced glucose intolerance and insulin resistance; it also affects mucosal barrier maintenance and the prevention of endotoxemia and chronic inflammation. We determine IL-22 levels in MetS patients and whether IL-22 is associated with MetS and its components. Material and Method: In this cross-sectional study, we measured serum IL-22 in 194 patients who had been newly diagnosed with MetS; we also employed 73 control patients. We used logistic regression analyses to evaluate the association of low serum levels of IL-22 with metabolic syndrome after adjusting for potential confounders. Results: Serum IL-22 concentrations were lower in subjects with MetS than in the controls. Serum IL-22 was negatively correlated with adiposity, fasting insulin, fasting glucose, C-reactive protein, triglycerides, and body mass index; it was positively correlated with HDL cholesterol. Logistic regression analysis demonstrated an independent association between serum IL-22 and metabolic syndrome. Discussion: These data suggested that decreased IL-22 levels are associated with MetS and its components and that IL-22 may be a novel biomarker in metabolic and endocrine regulations.

Keywords

IL-22; Metabolic Syndrome; Abdominal Obesity; Dyslipidemia; Inflammation; Insulin Resistance

DOI: 10.4328/JCAM.5725 Received: 30.01.2018 Accepted: 03.03.2018 Published Online: 03.03.2018 Printed: 01.07.2018 J Clin Anal Med 2018;9(4): 310-4
Corresponding Author: Hakki Yilmaz, Department of Internal Medicine, Section of Nephrology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Health Science University, Ankara, Turkey. T.: +90 3123360909 F.: +90 3123340352
ORCID ID: 0000-0001-5861-1865

Introduction

It is generally accepted that there is a link between an altered gut microbiota and metabolic disorders such as obesity, diabetes, and cardiovascular disease [1-3]. The disintegrity of mucosal barriers may lead to systemic endotoxemia that contributes to chronic low-grade inflammation, which further stimulates the development of metabolic syndrome (MetS) [3-5]. Interleukin-22 (IL-22) is a member of the IL-10 family of cytokines and is predominantly expressed by innate lymphoid cells and activated CD4+ T helper subsets such as T helper type 17 (TH17) and TH22 cells [6, 7]. IL-22 may exert multiple effects on the immune system and may be associated with the acute-phase response, activation of the innate immune system, induction of cell migration, inhibition of dendritic cell functions, and attenuation of allergic responses (7, 8). IL-22 plays a crucial role in eliciting antimicrobial immunity and ensuring maintenance of mucosal barrier integrity within the intestine or lungs [8, 9]. Mice deficient in IL-22 receptor and fed a high-fat diet are predisposed to developing metabolic disorders [10, 11]. Endogenous and exogenous IL-22 exerts a protective role in the destruction of insulin-producing beta cells from oxidative and endoplasmic reticulum (ER) stress [10, 11]. Administering IL-22 can decrease insulin resistance and stabilize blood glucose in diet induced obese (DIO) mice due to the restoration of beta-cell function and a decline in oxidative stress in the islet [10, 11]. We hypothesized that decreased levels of serum IL-22 would be associated with newly diagnosed MetS and its parameters, in accordance with findings in the literature. The purpose of this study was to investigate associations between serum IL-22 levels and the parameters of MetS in patients with newly diagnosed MetS.

Material and Method

Asymptomatic subjects (n=1541) were admitted for a general health screening at our Checkup unit of Internal Medicine (Ankara, Turkey) between November 2012 and June 2013. Nearly three-quarters of these asymptomatic subjects (n=1088) were excluded based on the exclusion criteria: an age below 18 or above 65 years, a body mass index (BMI) value > 40 kg/m2, medication targeting glucose or lipid metabolism, a history of or clinical evidence of cancer, type 2 diabetes, or cardiopulmonary, renal, or hepatic diseases. The subjects who satisfied the eligibility criteria (n=453) were screened for MetS. One hundred and ninety-four patients (n=194) with newly diagnosed MetS (cases) along with 73 healthy subjects matched by age and sex (controls) were consecutively recruited from these screened subjects. MetS was defined using the International Diabetes Federation (IDF) criteria for Europids [12] as a presentation of increased waist circumference (WC) ≥ 94 cm for men or ≥ 80 cm for women plus any two of the following: 1) triglycerides (TGs) ≥150 mg/dL; 2) high-density lipoprotein (HDL) cholesterol <40 mg/dL in men or <50 mg/dL in women; 3) blood pressure ≥130/85 mmHg or the current use of antihypertensive medications; and 4) fasting glucose ≥100 mg/dL [12]. The study was conducted in accordance with the Declaration of Helsinki. After the initial screening visit at our clinic and prior to blood sampling, all of the subjects selected were asked to sign a form of written informed consent to participate in this study; the protocol of this study had been previously approved by the Local Ethics Committee (IRB Number: 99950669/7).

We measured WC in centimeters without compression of the soft tissue midway between the lower rib margin and the iliac crest using a non-stretchable measuring tape. We also measured hip circumference in centimeters using the same measuring tape; we measured at the widest portion of the buttocks with the tape parallel to the floor. Both of these measurements were obtained while the subjects were standing with their feet close together, with their arms at their sides, and with their body weight evenly distributed. We collected these data when the subjects were wearing minimal clothing. We measured weight and height with the subjects wearing light clothing and no shoes; BMI was calculated as body weight (in kilograms) divided by the square of body height (in meters). We measured blood pressure (BP) using a standard adult arm cuff of a mercury-type sphygmomanometer after 10 minutes of rest in the clinic; the nurses working in the checkup unit made the BP measurements. To improve the reliability of the BP measurement, two readings were taken separated by one minute, and the average of the two readings was recorded as the final BP of the patient. However, if the difference between the two readings exceeded 5 mmHg, a third measurement was obtained and the average of the three readings was recorded as the final BP of the patient [13].

We collected blood samples at 8:00 a.m., after the patients had been fasting for at least 10 hours. Glucose, total cholesterol (TC), HDL cholesterol, TGs, and C-reactive protein (CRP) were measured using an autoanalyzer (Cobas Integra 800, Roche Diagnostics GmbH, Manheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using Friedwald's formula (for patients with a TG level below 400 mg/dL). We measured serum insulin levels with the chemiluminescent automated method (CLIA) Access (Beckman Coulter, Brea, CA, USA). Insulin resistance was estimated from homeostasis model assessment of insulin resistance (HOMA-IR) index [Fasting insulin(μU/mL) × Fasting glucose (mg/dL) / 405] [14].

We determined high sensitivity C-reactive protein (hs-CRP) in serum by using commercial ELISA kit (Catalog Number: MBS703598, MyBioSource, San Diego, CA, USA). The detection range was 0.625 ng/ml-40 ng/ml. The inter-assay coefficient of variability (CV) <10% and Intra-assay Precision (Precision within an assay): CV%<8%.

We measured serum IL-22 levels via ELISA (Human IL-22 Immunoassay Quantikine ELISA, Catalog Number: D2200, R&D Systems, Minneapolis, USA) on samples stored at −80°C according to the manufacturer's instructions. Minimum detectable dose (MDD) of IL-22 ranged from 0.7 pg/mL to 5.8 pg/mL. The mean MDD was 2.7 pg/mL, and the inter-assay coefficient of variability was 8.4%.

We express the data as mean ± standard deviation or median (interquartile range) when appropriate. We used the Kolmogorov-Smirnov test on continuous variables to check for distribution normality. Statistical comparisons were performed using independent-samples t tests for data with a normal distribution, Mann-Whitney U tests for data with a skewed distribution, and chi-squared tests for percentages. We calculated the Spearman rank correlation coefficient to

evaluate the correlation between IL-22 and age, sex, CRP, BMI, WC, fasting glucose, insulin, HOMA, TC, HDL cholesterol, LDL cholesterol, TGs, systolic BP (SBP), and diastolic BP (DBP), respectively. To evaluate the association of high serum levels of IL-22 with MetS, we controlled for variables initially associated with MetS and with IL-22 in the multiple logistic regression models. The final multivariate model includes all of the individual variables that were statistically significant. P values less than 0.05 were considered to be statistically significant. We used IBM SPSS Statistics Version 20 software (SPSS, Inc., Chicago, IL, USA) for the data analysis.

Results

The clinical and metabolic parameters of the patients with MetS and their matched controls are presented in Table 1. Consistent with the definition of the syndrome, the patients with MetS were obese, exhibited significantly larger WCs than the controls, and had higher levels of diastolic and systolic BP; in addition, they presented significantly higher levels of glucose and TGs as well as lower levels of HDL cholesterol at fasting compared with the controls. HOMA-IR and CRP levels were also significantly increased in patients with MetS. On the other hand, individuals with MetS had significantly lower serum IL-22 concentrations than the controls (39.61 ± 13.09 pg/mL vs 91.56 ± 17.62 pg/mL; P<0.01). We found that serum IL-22 concentrations were negatively correlated with WC (r = −0.763, P<0.001), fasting plasma glucose (FPG) (r = −0.856, P<0.001), fasting plasma insulin (r = −0.817, P<0.001), HOMA-IR (r = −0.846, P<0.001) (Figure 1), BMI (r = −0.682, P<0.001), hs-CRP (r = -0.568, P<0.001) (Figure 2), and serum TG levels (r = −0.297, P = 0.03). IL-22 was correlated with HDL cholesterol (r = 0.684, P<0.001). We did not find any relation between

Table 1. Clinical and biochemical characteristics in control subjects and in patients with MetS.

	Controls (n=73)	MetS patients (n=194)	P value
Age (years)	38.5 ± 9.8	39.1 ± 10.2	0.714
Male sex n (%)	21 (28.7)	58 (29.8)	0.301
Smoking n (%)	14 (19.1)	38 (19.5)	0.847
Waist circumference (cm)	87.68 ± 7.45	104.57 ± 10.04	<0.01
BMI (kg/m^2)	23.99 ± 2.07	29.29 ± 2.58	<0.01
SBP (mmHg)	138 ± 9	118 ± 5	<0.01
DBP (mmHg)	86 ± 6	73 ± 5	<0.01
FPG (mg/dL)	86.25 ± 4.28	104.81 ± 8.24	<0.01
Fasting plasma insulin (μU/mL)	9.20 ± 2.13	14.81 ± 2.04	<0.01
HOMA-IR	1.96 ± 0.47	3.86 ± 0.77	<0.01
TC (mg/dL)	196.87 ± 38.02	197.54 ± 32.71	0.479
TG (mg/dL)	98.36 ± 19.58	221.60 ± 52.05	<0.01
LDL-C (mg/dL)	118.32 ± 28.90	118.41 ± 29,36	0.684
HDL-C (mg/dL)	57.87 ± 9.55	34.80 ± 5.09	<0.01
hs-CRP (ng/mL)	1.55 ± 0.33	3.53 ± 1.13	<0.01
Serum IL-22 levels (pg/mL)	91.56 ± 17.62	39.61 ± 13.09	<0.01

Abbreviations: BMI, body mass index; CRP, C-reaction protein; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

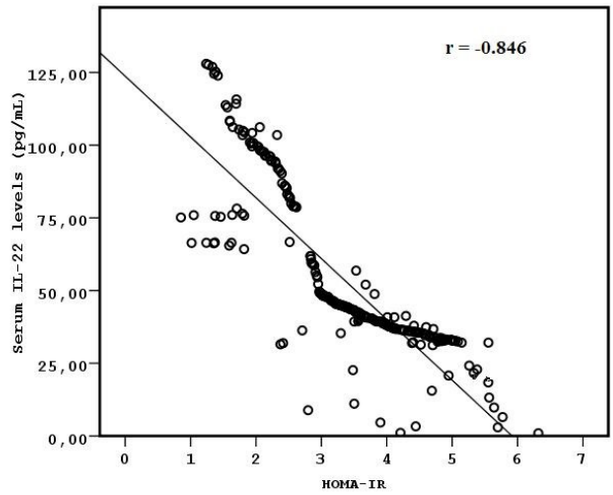

Figure 1. Serum IL-22 levels were inversely related to HOMA-IR.

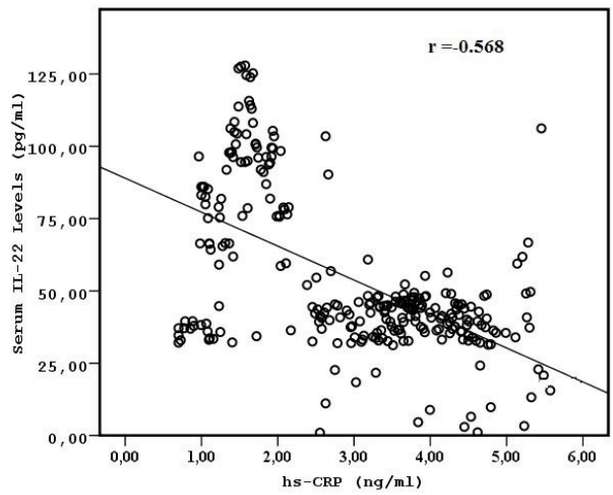

Figure 2. There was an inverse association between serum IL-22 levels and hs-CRP

serum IL-22 concentration and SBP and/or DBP. In addition, we did not observe a correlation between IL-22 concentrations and age, sex, TC, or LDL cholesterol, respectively. We tested the difference in IL-22 concentrations between patients with MetS and the controls for potential confounding variables such as age, sex, WC, BMI, glucose, insulin, HOMA index, TC, HDL cholesterol, LDL cholesterol, TGs, SBP, DBP, and CRP. IL-22 was still significantly associated with MetS (P = 0.008) after adjusting for HOMA index, WC, and HDL cholesterol. Discussion We report, for the first time, that low IL-22 concentrations are associated with MetS, independent of several confounders. In addition, our correlation analysis demonstrated a strong inverse correlation of serum IL-22 levels with several parameters of adiposity (BMI, WC), insulin resistance (increased fasting insulin and HOMA-IR), and adverse lipid profiles (increased TGs and decreased HDL cholesterol). Abdominal obesity, dyslipidemia, low-grade inflammation, and insulin resistance were the primary contributors to this association. These findings suggest that IL-22 may play a role in the pathophysiology of metabolic disorders such as MetS. Recent evidence from experimental studies suggests that IL-22 is a potent metabolic regulator with multiple beneficial effects on obesity and obesity-induced metabolic

disorders [10,11]. Direct administration of recombinant IL-22 has been shown to alleviate hyperglycemia, hyperinsulinemia, and dyslipidemia in DIO mice [10, 11]. In some mouse models the overexpression or administration of IL-22 was associated with supra-physiological circulating levels (well above 1000 pg/ml) [15, 16]. It is likely that the body weight reducing effect described was due to a potent anorectic effect and super high levels of IL-22 promote cachexia by using mechanisms similar to those used by some cytokines (TNF-α, IL-6, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and interferon-γ), such as induction of strong acute-phase response and subsequent chronic inflammation [16]. However, the clinical relevance of these findings has never been explored. In this study, we provide the first clinical evidence that serum levels of IL-22, which have been suggested as potential candidates for the treatment of obesity-related metabolic disorders. The relation between MetS and inflammation is well established, and a proinflammatory state is accepted as a major contributor to the development of MetS [17-20]. We found that low levels of IL-22 in MetS are linked to a chronic, low-grade inflammatory state. In contrast to our results, the overexpression of IL-22 has been observed in several different chronic inflammatory conditions, including psoriasis, inflammatory bowel disease, and rheumatoid arthritis [21-23]. Transgenic overexpression of IL-22 in mice results in characteristic epidermal alterations that resemble psoriasis [24]. Moreover, Zheng et al. revealed that IL-23- induced acanthosis and dermal inflammation were significantly decreased in IL-22-deficient mice [25]. IL-22 was also shown to play a proinflammatory role in an animal model of rheumatoid arthritis [26]. On the other hand, IL-22 exerts a protective role in some inflammatory conditions such as hepatitis and inflammatory bowel disease [27-29]. We observed an inverse correlation between IL-22 levels and FPG and insulin. We hypothesized that decreased levels of IL-22 would be associated with the development of diabetes. Two recent studies in mice have shown that endogenous and exogenous IL-22 was able to reverse hyperglycemia and insulin resistance and preserve the integrity of mucosal barriers, resulting in improved glycemic control via a reduction of beta cell oxidative and ER stress [10, 11]. In addition, IL-22 leads to an upregulation of Reg gene expression that can be related to β-cell regeneration and the reversal of hyperglycemia in type 1 diabetes [30, 31]. However, two clinical studies have found that the concentrations of IL-22 in serum and plasma were elevated in patients with type 2 diabetes mellitus [32, 33]. Our data appear to be consistent with these two experimental studies [10, 11]. Our data suggest that decreased levels of IL-22 are associated with the development of diabetes. We propose that there is an association between IL-22 and dyslipidemia via insulin resistance. People who are insulin resistant often have dyslipidemia, which is characterized by elevated levels of TGs, low HDL cholesterol, and small, dense LDL particles. It is known that insulin resistance can result in insensitivity to the antilipolytic effect of insulin in adipose tissue; insulin resistance may lead to high serum free fatty acid concentrations in the circulation [34]. Wang et al. revealed that IL-22Fc was involved in the modulation of lipid metabolism in
db/db and DIO mice by enhancing lipolysis and fatty acid β-oxidation via signal transducer and activator of transcription 3 activation in adipose tissue, primary adipocytes, and hepatocytes [11]. IL-22-related fat store mobilization results in a decreased white adipose tissue TG concentration, liver steatosis, and circulating TGs and free fatty acids [11]. Increased IL-22 levels appear to attenuate atherogenic lipid profile, which is inconsistent with our results. However, a recent experimental study revealed that elevated IL-22 levels were associated with the promotion of atherosclerosis and increased lipid content via decreased ABCG1 expression and reduced cholesterol efflux in foam cells [35]. We did not recover any relation between IL-22 and dyslipidemia after accounting for confounding variables in our multivariate analysis. Our data suggest the hypothesis that decreased IL-22 levels may contribute to the development of atherogenic lipid profiles that include hypertriglyceridemia, low serum HDL cholesterol concentrations, and coronary disease via insulin resistance and fat store immobilization in MetS. It is important to note the limitations of this study. First, because of the cross-sectional research design of our investigation, we were unable to determine the cause and effect between IL-22 and MetS in the present study; we do not provide a temporal interpretation of the reported associations. Second, even though the normoglycemic hyperinsulinemic clamp technique (glucose clamp) is the standard method for evaluating the degree of insulin resistance, we used HOMA-IR to estimate insulin resistance in this study. Third, our analyses are based on single measurements of blood IL-22, which may not reflect IL-22 levels over time. Serial changes in serum IL-22 need to be measured in patients with newly diagnosed MetS to further clarify the role of IL-22 in the pathogenesis of MetS. Fourthly, our study included a relatively small patient cohort, which might have limited the strength of our results. In conclusion, decreased levels of IL-22 are related to MetS and its components. IL-22 may be a strong and novel biomarker for the regulation of glucose and lipid metabolism. Decreased levels of IL-22 may play a role in the development of abdominal obesity, dyslipidemia, low-grade inflammation, and insulin resistance.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Yilmaz H. Decreased circulating levels of il-22 in newly diagnosed metabolic syndrome patients. J Clin Anal Med 2018;9(4): 310-4.